World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5306/wjco.v5.i2.149

World J Clin Oncol 2014 May 10; 5(2): 149-155
ISSN 2218-4333 (online)

MINIREVIEWS

Bone metastases: When and how lung cancer interacts with bone

Ilaria Roato

Ilaria Roato, CeRMS, AO Città della Salute e della Scienza di Torino, Department of Medical Science, University of Turin, 10126 Torino, Italy
Author contributions: Roato I contributed to the conception, literature analysis, drafting and revising of this review.
Supported by Italian Ministry of Health: Ricerca Sanitaria Finalizzata e Giovani Ricercatori 2009, No. GR 2009-1584485
Correspondence to: Ilaria Roato, PhD, CeRMS, AO Città della Salute e della Scienza di Torino, Department of Medical Science, University of Turin, Via Santena 5, 10126 Torino, Italy. roato78@libero.it
Telephone: +39-11-6334672 Fax: +39-11-6334672
Received: December 27, 2013 Revised: February 21, 2014
Accepted: March 17, 2014
Published online: May 10, 2014

Abstract

Bone metastasis is a common and debilitating consequence of lung cancer: 30%-40% of patients with non-small cell lung cancer develop bone metastases during the course of their disease. Lung cancer cells find a favorable soil in the bone microenvironment due to factors released by the bone matrix, the immune system cells, and the same cancer cells. Many aspects of the cross-talk among lung tumor cells, the immune system, and bone cells are not clear, but this review aims to summarize the recent findings in this field, with particular attention to studies conducted to identify biomarkers for early detection of lung cancer bone metastases.

Key words: Lung cancer; Bone metastases; Osteoclast; T cell; Bone microenvironment

Core tip: This review reports current knowledge on the cross-talk among lung tumor cells, the bone microenvironment, and the immune system, that lead to bone metastasis.

Roato I. Bone metastases: When and how lung cancer interacts with bone. *World J Clin Oncol* 2014; 5(2): 149-155 Available from: URL: http://www.wjgnet.com/2218-4333/full/v5/i2/149.htm DOI: http://dx.doi.org/10.5306/wjco.v5.i2.149

INTRODUCTION

Lung cancer is the most common tumor worldwide, and in Europe alone, it is responsible for the 20.6% of cancer mortality[1]. It has poor overall survival rates: the majority of advanced stage lung cancer patients die within 18 mo from diagnosis[2]. The predominant form of lung cancer is non-small cell lung cancer (NSCLC), and is responsible for 80%-85% of all lung tumors[3].

Lung cancer frequently metastasizes to bone, with 36% of patients presenting with bone lesions at autopsy[4] and 22%-60% showing bone marrow micro-metastases[5]. The early diagnosis of NSCLC is difficult, and 30%-40% of patients with NSCLC develop bone metastases during the course of their disease[6,7]. The prognosis of lung cancer patients with bone metastases is poor, with a median survival time from detection of lesions measured in months[4]. Even though NSCLC patients have a relatively short survival time, a large percentage develop skeletal-related events (SREs), thus clinicians show particular attention to the management of bone metastases to prevent debilitating skeletal complications. Indeed, bone metastases are often not diagnosed in NSCLC patients until they cause pain and SREs[8], but once a patient has a first SRE, he is likely to experience subsequent events, leading to debilitating bone lesions and a reduction in the quality of life. Lung cancer bone metastases normally appear as areas of radiolucency and are osteolytic, with poor margination, no matrix and cortical destruction[9]. They commonly affect the spine, ribs, pelvis and proximal long bones. At an early stage, bone metastases may occur easily at an axial bone through the vertebral vein system, then at appendicular bone in more advanced

stages of the disease[10]. A unique feature of this tumor is the ability to spread to the bones of the hands and feet. This is probably due to the ability of lung cancer to shed malignant cells directly into the arterial blood flow, from where they can be seeded far and wide.

In this review, I summarize the current knowledge on the cross-talk among lung tumor cells, the bone microenvironment, and the immune system, that lead to bone metastasis formation.

BONE MICROENVIRONMENT IS A FERTILE SOIL FOR DORMANT AND PROLIFERATING TUMOR CELLS

Tumor dissemination is an early event and is not related to the size of the tumor mass, supporting the idea of concomitant progression of the primary tumor and metastasis[11]. Several studies have shown that disseminated cells, shed from a primary tumor, may lie dormant in distant tissues for long periods before they can be activated to form metastases. The skeleton has a large surface area and a microenvironment conducive and protective to tumor cell growth. Indeed, disseminated tumor cells (DTCs) can persist in a quiescent state in the bone marrow of cancer patients for years, particularly if they lie in the hematopoietic stem cell (HSC) niche[12], which expresses adhesion molecules and secretes factors contributing to tumor cell dormancy. At present, it is not clear how dormancy is induced or what leads to activation of the dormant cells. One hypothesis is that molecules that induce HSC dormancy are likely to induce dormancy of metastatic tumor cells[13]. For instance, osteoblasts (OBs) which are a crucial component of the stem cell niche, express stromal derived factor-1 (SDF-1) and annexin-Ⅱ (Anxa2), that attract both HSCs and cancer cells expressing their receptors, CXCR4 and Anxa2r, respectively[14]. In this way, the niche attracts, protects and induces dormancy of DTCs, which may be released from quiescence and grow as a consequence of a stimulatory microenvironment, like bone. DTCs detected in bone marrow of breast cancer patients exhibited features of mesenchymal and cancer initiating cells (CICs)[15]. These latter cells are responsible for both primary tumor generation, maintenance, recurrence and drug resistance[16,17]. In lung cancer, a subset of cells expressing CD133 and CXCR4 has been shown to have CIC features and to be essential for tumor metastasis formation[18]. Moreover, chemotherapy may select resistant CICs[19], as also demonstrated by Bertolini *et al*[20] who showed that lung CICs developed resistance to cisplatin. The monitoring of DTCs is a potential method to follow the dissemination of tumors, but a recent work reported that in NSCLC patients, DTC detection is not particularly useful to determine the presence of the disseminated disease in its early stages[21].

Bone has physical properties such as low pH, hypoxia and high levels of extracellular calcium[22], which sustain the proliferating tumor cells that secrete high quantities of lactic acid, creating a local area of bone with a low pH, which stimulates osteoclasts (OCs) activity. On the other hand, tumor cells grow better with a low pH and release proteolytic enzymes, that maintain the low pH, thus tumor expansion is perpetuated[23]. The active bone resorption causes an increase in extracellular calcium level that stimulates the calcium-sensing receptors on surrounding cells and tumor cells, leading to an increased secretion of parathyroid hormone-related peptide (PTHrP), a potent stimulator of OCs[24,25]. Bone is a hypoxic tissue, thus it promotes the ability of cancer cells to grow under hypoxic conditions, stimulating the expression of hypoxia inducible factor-1 (HIF-1). HIF-1 activates the transcription of target genes which encode proteins that play important roles in many critical aspects of cancer biology[26]. For instance, HIF-1 is involved in many steps of breast cancer metastasis, including metastatic niche formation, recruitment of bone marrow-derived cells to the metastatic niche, OC formation and OB inhibition[27-29].

FACTORS PRODUCED BY BONE AND TUMOR CELLS MODULATE OC ACTIVITY

The interaction of tumor and bone cells induces the formation of a vicious cycle leading to bone metastases[30]. Indeed, tumor cells disrupt normal bone remodeling, a perfectly balanced activity of bone resorption by OCs and bone formation by OBs. Bone resorption induced by cancer cells creates a physical space for tumor expansion, and it induces the release of growth factors and cytokines supporting tumor metastasis[31].

Bone marrow produces factors, such as SDF-1, which attracts cancer cells expressing the chemokine receptors, CXCR4 and CXCR7, thus it represents a favorable soil for secondary tumor localization[32,33]. Moreover, activated OCs resorb bone and release growth factors enmeshed in the bone matrix, such as bone morphogenetic proteins, transforming growth factor-β (TGF-β), insulin-like growth factor (IGF), fibroblast growth factor and others that stimulate the growth of metastatic tumor cells in bone, and the production and release of bone resorbing factors from tumor cells[34,35]. In particular, TGF-β stimulates HIF-1 signaling within bone, contributing to the vicious cycle driving the development of metastatic osteolysis[36]. Malignant cells produce cytokines, such as interleukin-6 (IL-6), IL-8 and IL-11, which activate OCs[37]. IL-6 can stimulate tumor cell proliferation, migration and invasion of lung and other tumors[38,39], and it may induce bone resorption or formation according to the interactions with other factors like PTHrP, IL-1 and receptor activator of nuclear factor-kB ligand (RANKL). IL-8 stimulates OC maturation through binding with its receptor CXCR1 expressed on OC precursors[40]. IL-11 stimulates osteoclastogenesis and it has been reported to be a predictive factor for development of osteolytic bone metastasis[41]. Cancer cells also secrete molecules such as parathyroid hormone, PTHrP, prostaglandins, activated vitamin D and TNF, which stimulate RANKL expression on OBs and bone marrow stromal cells[42].

RANK, the RANKL receptor, is expressed by solid tumors, with high concordance between bone metastasis and corresponding primary tumors[43]. The activation of the RANK/RANKL axis leads to an increase in OC number, survival and activity, and it may induce migration and homing of tumor cells to the RANKL-rich bone microenvironment[44]. In clinical practice the use of target therapy to reduce bone metastases gave encouraging results: the fully human monoclonal antibody directed against RANKL reduces bone metastases in breast and lung tumors[45-47]. Nuclear factor-kappa B is the downstream target of RANKL and it is also activated in lung cancer cells by epidermal growth factor receptor (EGFR), implicating this pathway as pivotal in lung cancer bone metastases[46]. EGFR-tyrosine kinase inhibitors (TKIs), such as erlotinib, show dramatic anti-tumor activity in a subset of NSCLC patients with an active mutation in the *EGFR* gene. Some lung cancer patients with wild type EGFR respond to EGFR-TKIs, thus EGFR-TKIs have an effect on host cells as well as tumor cells, preventing bone metastases by affecting the host microenvironment irrespective of its direct effect on tumor cells[48].

PTHrP promotes OC bone resorption[49-51], and it stimulates OBs and stromal cells to express RANKL, which induces OC maturation[52,53]. Among the inhibitors of PTHrP, recent data report that the microRNA miR-33a is downregulated in lung cancer cells, and it directly targets PTHrP leading to decreased osteolytic bone metastasis[54]. Indeed, the downregulation of PTHrP, induced by miR-33a, causes a decreased secretion of IL-8, with consequent reduction in OC differentiation and bone resorption[54]. Novel data derived from a pre-clinical model of NSCLC reports that miR335 inhibits the expression of RANKL and IGF-1 receptor by lung cancer cells, thus skeletal metastasis is reduced[55].

In the bone marrow, a direct activation of osteolysis by cancer cells has been shown through the interaction between Notch and Jagged. Jagged1, a downstream mediator of the pro-metastatic TGF-β, promotes tumor growth through stimulation of IL-6 production from OBs, and directly activates OC differentiation[56]. Moreover, Jagged is overexpressed by bone metastatic tumor cells[57], whereas its receptor Notch is frequently expressed by progenitors and mature cells in the bone marrow[58]. In breast cancer, Notch-Jagged interactions activate biological responses in OCs and OBs, which promote both tumor invasion of bone and tumor cell growth in bone[56]. In NSCLC, the expression of Notch-3 receptor correlates with a poor prognosis and the stage of the disease[59].

ROLE OF IMMUNE SYSTEM CELLS IN REGULATION OF OCS AND TUMOR GROWTH IN BONE

Oxidative stress is implicated in the initiation and progression of lung cancer[60]. In particular, myeloid-derived suppressor cells (MDSC), which infiltrate different tumors, generate reactive oxygen species (ROS) and cytokines, that suppress host T cell responses, promoting tumor progression and metastasis[61]. Both the production of ROS and nitric oxide are involved in osteoclastogenesis, and bone marrow-derived MDSCs have been showed to be able to differentiate into OCs; thus, all these factors contribute to enhanced bone destruction in tumor osteolysis[62,63].

Direct involvement of T cells in regulating OC activity has been demonstrated in patients affected by multiple myeloma, lung cancer and other solid tumors with bone metastasis[64-67]. These bone metastatic patients showed an increase in circulating OC precursors compared with both healthy controls and cancer patients without bone metastases[66]. OC precursors differentiate into mature, multinucleated and bone resorbing OCs *in vitro*, without adding exogenous pro-osteoclastogenic factors, such as TNF-α and RANKL, which instead are released by T cells. Cell cultures of PBMCs derived from cancer patients without bone metastasis, and depleted of T cells, do not differentiate into OCs without adding macrophage colony stimulating factor and RANKL[65,66], confirming that T cells regulate osteoclastogenesis and play an important role in the cancer cycle of bone destruction.

Recently, it has been demonstrated that T cells are additional regulators of bone tumor growth. In particular, their activation diminishes bone metastases, whereas their depletion enhances them, even in the presence of zoledronic acid[68]. Indeed, some patients treated with antiresorptive therapies develop further skeletal metastases, suggesting that T cells modulate bone tumor growth. Zoledronic acid can activate cytotoxic γ/δ-T cells and inhibit populations of myeloid-derived cells with T-cell-suppressor capabilities[69]. The anti-bone metastatic therapy based on the blockade of TGF-β at metastatic sites may locally activate an anti-tumor T cell response, because normally TGF-β, released in bone marrow by OC activity, inhibits T cell proliferation[70]. Tumor cell-derived IL-6, IL-1 and TGF-β can drive T-cell differentiation towards a Th17 secretory helper-cell phenotype able to induce RANKL production by OB and OC activation through IL-17 production[71]. All these data demonstrate the fundamental role of immune system cells in the control of bone metastatic disease.

SERUM MARKERS FOR EARLY DETECTION OF LUNG CANCER BONE METASTASES

The delayed demonstration of skeletal involvement may seriously affect survival, thus an early diagnosis of bone metastases is necessary. The early detection of asymptomatic bone disease due to lung cancer can be obtained through positron-emission tomography scans[72], but European guidelines recommend a bone scan only in the presence of bone pain[3], thus other systems for an early diagnosis are required. The sensitivity of common serum tumor markers is low, and they are used mainly for monitoring the efficacy of therapy and detection of

recurrence. The use of serological markers is desirable, but unfortunately, the identification of potentially useful and specific biomarkers is difficult. According to data in the literature, serum markers of bone turnover may be able to determine the time to tumor progression, the metastatic potential, and the overall survival of NSCLC patients. Furthermore, they may contribute to a more accurate follow-up and tailored treatment options[73,74]. In particular, there is a statistically significant relationship between levels of biochemical markers of bone metabolism and clinical outcome: both N-telopeptide and bone-specific alkaline phosphatase levels were highly predictive of SRE recurrence, the time to a first SRE, and the occurrence of disease progression and death[7,75]. Also, the carboxy-terminal telopeptide of type I collagen and amino-terminal propeptide of type I collagen measurement can be useful in monitoring patients with NSCLC during follow-up, with the aim of detecting bone metastases early[76].

Among the molecules potentially involved in the pathogenesis of bone metastases from lung cancer, there is IL-7, which has been studied as serum marker for monitoring bone metastasis development in NSCLC patients. Indeed, IL-7 is an important regulator of the interaction between bone and immune system, and it has a role in bone homeostasis, in particular in bone loss in estrogen-deficient conditions[77,78], psoriatic arthritis[79] and periodontitis[80]. Other studies support an active role of IL-7 in promoting bone lesions from solid tumors[81,82] and multiple myeloma[83]. In culture of PBMCs derived from patients with bone metastases due to lung cancer and other solid tumors, IL-7 was mainly released by B cells, and it directly sensitized T cells to produce pro-osteoclastogenic factors, such as tumor necrosis factor-α and RANKL, which enhanced osteoclastogenesis[82,83]. Moreover, in lung cancer patients with bone metastases, IL-7 serum levels were found to be significantly higher than in non-bone metastatic patients and in healthy controls[84]. This increase in serum IL-7 directly depends on tumor production, and indeed strong IL-7 expression was detected in human tumor masses in a mouse model of bone metastases and in human bone metastatic biopsies[85]. Further studies on a large cohort of patients needs to be performed, but IL-7 could be very useful to monitor the progression and early development of lung cancer bone disease.

CONCLUSION

The current literature reports the existence of an important interaction among lung tumor cells, the bone microenvironment and immune system cells. Many factors are involved in this cross-talk, which may lead to the discovery of new biomarkers useful for early detection of lung cancer bone metastases.

REFERENCES

1 **Brenner H**, Francisci S, de Angelis R, Marcos-Gragera R, Verdecchia A, Gatta G, Allemani C, Ciccolallo L, Coleman M, Sant M. Long-term survival expectations of cancer patients in Europe in 2000-2002. *Eur J Cancer* 2009; **45**: 1028-1041 [PMID: 19091549 DOI: 10.1016/j.ejca.2008.11.005]

2 **Langer CJ**, Besse B, Gualberto A, Brambilla E, Soria JC. The evolving role of histology in the management of advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 5311-5320 [PMID: 21079145 DOI: 10.1200/JCO.2010.28.8126]

3 **D'Addario G**, Früh M, Reck M, Baumann P, Klepetko W, Felip E. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** Suppl 5: v116-v119 [PMID: 20555059 DOI: 10.1093/annonc/mdq189]

4 **Coleman RE**. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006; **12**: 6243s-6249s [PMID: 17062708 DOI: 10.1158/1078-0432.CCR-06-0931]

5 **Coello MC**, Luketich JD, Litle VR, Godfrey TE. Prognostic significance of micrometastasis in non-small-cell lung cancer. *Clin Lung Cancer* 2004; **5**: 214-225 [PMID: 14967073 DOI: 10.3816/CLC.2004.n.002]

6 **Tsuya A**, Kurata T, Tamura K, Fukuoka M. Skeletal metastases in non-small cell lung cancer: a retrospective study. *Lung Cancer* 2007; **57**: 229-232 [PMID: 17451841 DOI: 10.1016/j.lungcan.2007.03.013]

7 **Al Husaini H**, Wheatley-Price P, Clemons M, Shepherd FA. Prevention and management of bone metastases in lung cancer: a review. *J Thorac Oncol* 2009; **4**: 251-259 [PMID: 19179905 DOI: 10.1097/JTO.0b013e31819518fc]

8 **Iordanidou L**, Trivizaki E, Saranti S, Georgakopoulos A, Bolanos N, Baltagiannis N, Koutsiouba P. Is there a role of whole body bone scan in early stages of non small cell lung cancer patients. *J BUON* 2006; **11**: 491-497 [PMID: 17309183]

9 **Coleman RE**. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001; **27**: 165-176 [PMID: 11417967 DOI: 10.1053/ctrv.2000.0210]

10 **Batson OV**. The function of the vertebral veins and their role in the spread of metastases. *Ann Surg* 1940; **112**: 138-149 [PMID: 17857618 DOI: 10.1097/00000658-194007000-00016]

11 **Hüsemann Y**, Geigl JB, Schubert F, Musiani P, Meyer M, Burghart E, Forni G, Eils R, Fehm T, Riethmüller G, Klein CA. Systemic spread is an early step in breast cancer. *Cancer Cell* 2008; **13**: 58-68 [PMID: 18167340 DOI: 10.1016/j.ccr.2007.12.003]

12 **Luzzi KJ**, MacDonald IC, Schmidt EE, Kerkvliet N, Morris VL, Chambers AF, Groom AC. Multistep nature of metastatic inefficiency: dormancy of solitary cells after successful extravasation and limited survival of early micrometastases. *Am J Pathol* 1998; **153**: 865-873 [PMID: 9736035 DOI: 10.1016/S0002-9440(10)65628-3]

13 **Shiozawa Y**, Pedersen EA, Patel LR, Ziegler AM, Havens AM, Jung Y, Wang J, Zalucha S, Loberg RD, Pienta KJ, Taichman RS. GAS6/AXL axis regulates prostate cancer invasion, proliferation, and survival in the bone marrow niche. *Neoplasia* 2010; **12**: 116-127 [PMID: 20126470]

14 **Shiozawa Y**, Havens AM, Jung Y, Ziegler AM, Pedersen EA, Wang J, Wang J, Lu G, Roodman GD, Loberg RD, Pienta KJ, Taichman RS. Annexin II/annexin II receptor axis regulates adhesion, migration, homing, and growth of prostate cancer. *J Cell Biochem* 2008; **105**: 370-380 [PMID: 18636554 DOI: 10.1002/jcb.21835]

15 **Aktas B**, Tewes M, Fehm T, Hauch S, Kimmig R, Kasimir-Bauer S. Stem cell and epithelial-mesenchymal transition markers are frequently overexpressed in circulating tumor cells of metastatic breast cancer patients. *Breast Cancer Res* 2009; **11**: R46 [PMID: 19589136]

16 **Creighton CJ**, Li X, Landis M, Dixon JM, Neumeister VM, Sjolund A, Rimm DL, Wong H, Rodriguez A, Herschkowitz JI, Fan C, Zhang X, He X, Pavlick A, Gutierrez MC, Renshaw L, Larionov AA, Faratian D, Hilsenbeck SG, Perou CM, Lewis MT, Rosen JM, Chang JC. Residual breast cancers after conventional therapy display mesenchymal as well as tumor-ini-

tiating features. *Proc Natl Acad Sci USA* 2009; **106**: 13820-13825 [PMID: 19666588 DOI: 10.1073/pnas.0905718106]
17 **Zhou BB**, Zhang H, Damelin M, Geles KG, Grindley JC, Dirks PB. Tumour-initiating cells: challenges and opportunities for anticancer drug discovery. *Nat Rev Drug Discov* 2009; **8**: 806-823 [PMID: 19794444 DOI: 10.1038/nrd2137]
18 **Hermann PC**, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, Bruns CJ, Heeschen C. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. *Cell Stem Cell* 2007; **1**: 313-323 [PMID: 18371365 DOI: 10.1016/j.stem.2007.06.002]
19 **Singh A**, Settleman J. EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. *Oncogene* 2010; **29**: 4741-4751 [PMID: 20531305 DOI: 10.1038/onc.2010.215]
20 **Bertolini G**, Roz L, Perego P, Tortoreto M, Fontanella E, Gatti L, Pratesi G, Fabbri A, Andriani F, Tinelli S, Roz E, Caserini R, Lo Vullo S, Camerini T, Mariani L, Delia D, Calabrò E, Pastorino U, Sozzi G. Highly tumorigenic lung cancer CD133+ cells display stem-like features and are spared by cisplatin treatment. *Proc Natl Acad Sci USA* 2009; **106**: 16281-16286 [PMID: 19805294 DOI: 10.1073/pnas.0905653106]
21 **Rud AK**, Borgen E, Mælandsmo GM, Flatmark K, Le H, Josefsen D, Solvoll I, Schirmer CB, Helland Å, Jørgensen L, Brustugun OT, Fodstad Ø, Boye K. Clinical significance of disseminated tumour cells in non-small cell lung cancer. *Br J Cancer* 2013; **109**: 1264-1270 [PMID: 23942067 DOI: 10.1038/bjc.2013.450]
22 **Kingsley LA**, Fournier PG, Chirgwin JM, Guise TA. Molecular biology of bone metastasis. *Mol Cancer Ther* 2007; **6**: 2609-2617 [PMID: 17938257 DOI: 10.1158/1535-7163.MCT-07-0234]
23 **Arnett TR**. Extracellular pH regulates bone cell function. *J Nutr* 2008; **138**: 415S-418S [PMID: 18203913]
24 **Sharan K**, Siddiqui JA, Swarnkar G, Chattopadhyay N. Role of calcium-sensing receptor in bone biology. *Indian J Med Res* 2008; **127**: 274-286 [PMID: 18497443]
25 **Sanders JL**, Chattopadhyay N, Kifor O, Yamaguchi T, Butters RR, Brown EM. Extracellular calcium-sensing receptor expression and its potential role in regulating parathyroid hormone-related peptide secretion in human breast cancer cell lines. *Endocrinology* 2000; **141**: 4357-4364 [PMID: 11108243]
26 **Semenza GL**. Cancer-stromal cell interactions mediated by hypoxia-inducible factors promote angiogenesis, lymphangiogenesis, and metastasis. *Oncogene* 2013; **32**: 4057-4063 [PMID: 23222717 DOI: 10.1038/onc.2012.578]
27 **Wong CC**, Gilkes DM, Zhang H, Chen J, Wei H, Chaturvedi P, Fraley SI, Wong CM, Khoo US, Ng IO, Wirtz D, Semenza GL. Hypoxia-inducible factor 1 is a master regulator of breast cancer metastatic niche formation. *Proc Natl Acad Sci USA* 2011; **108**: 16369-16374 [PMID: 21911388 DOI: 10.1073/pnas.1113483108]
28 **Wong CC**, Zhang H, Gilkes DM, Chen J, Wei H, Chaturvedi P, Hubbi ME, Semenza GL. Inhibitors of hypoxia-inducible factor 1 block breast cancer metastatic niche formation and lung metastasis. *J Mol Med* (Berl) 2012; **90**: 803-815 [PMID: 22231744 DOI: 10.1007/s00109-011-0855-y]
29 **Hiraga T**, Kizaka-Kondoh S, Hirota K, Hiraoka M, Yoneda T. Hypoxia and hypoxia-inducible factor-1 expression enhance osteolytic bone metastases of breast cancer. *Cancer Res* 2007; **67**: 4157-4163 [PMID: 17483326 DOI: 10.1158/0008-5472.CAN-06-2355]
30 **Paget S**. The distribution of secondary growths in cancer of the breast. 1889. *Cancer Metastasis Rev* 1989; **8**: 98-101 [PMID: 2673568 DOI: 10.1016/S0140-6736(00)49915-0]
31 **Mundy GR**. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer* 2002; **2**: 584-593 [PMID: 12154351 DOI: 10.1038/nrc867]
32 **Salcedo R**, Oppenheim JJ. Role of chemokines in angiogenesis: CXCL12/SDF-1 and CXCR4 interaction, a key regulator of endothelial cell responses. *Microcirculation* 2003; **10**: 359-370 [PMID: 12851652 DOI: 10.1080/mic.10.3-4.359.370]
33 **Wang J**, Shiozawa Y, Wang J, Wang Y, Jung Y, Pienta KJ, Mehra R, Loberg R, Taichman RS. The role of CXCR7/RDC1 as a chemokine receptor for CXCL12/SDF-1 in prostate cancer. *J Biol Chem* 2008; **283**: 4283-4294 [PMID: 18057003 DOI: 10.1074/jbc.M707465200]
34 **Jakowlew SB**. Transforming growth factor-beta in cancer and metastasis. *Cancer Metastasis Rev* 2006; **25**: 435-457 [PMID: 16951986 DOI: 10.1007/s10555-006-9006-2]
35 **Stover DG**, Bierie B, Moses HL. A delicate balance: TGF-beta and the tumor microenvironment. *J Cell Biochem* 2007; **101**: 851-861 [PMID: 17486574 DOI: 10.1002/jcb.21149]
36 **McMahon S**, Charbonneau M, Grandmont S, Richard DE, Dubois CM. Transforming growth factor beta1 induces hypoxia-inducible factor-1 stabilization through selective inhibition of PHD2 expression. *J Biol Chem* 2006; **281**: 24171-24181 [PMID: 16815840 DOI: 10.1074/jbc.M604507200]
37 **Rose AA**, Siegel PM. Breast cancer-derived factors facilitate osteolytic bone metastasis. *Bull Cancer* 2006; **93**: 931-943 [PMID: 16980236]
38 **Hernández I**, Moreno JL, Zandueta C, Montuenga L, Lecanda F. Novel alternatively spliced ADAM8 isoforms contribute to the aggressive bone metastatic phenotype of lung cancer. *Oncogene* 2010; **29**: 3758-3769 [PMID: 20453887 DOI: 10.1038/onc.2010.130]
39 **Blanchard F**, Duplomb L, Baud'huin M, Brounais B. The dual role of IL-6-type cytokines on bone remodeling and bone tumors. *Cytokine Growth Factor Rev* 2009; **20**: 19-28 [PMID: 19038573 DOI: 10.1016/j.cytogfr.2008.11.004]
40 **Bendre MS**, Montague DC, Peery T, Akel NS, Gaddy D, Suva LJ. Interleukin-8 stimulation of osteoclastogenesis and bone resorption is a mechanism for the increased osteolysis of metastatic bone disease. *Bone* 2003; **33**: 28-37 [PMID: 12919697 DOI: 10.1016/S8756-3282(03)00086-3]
41 **Zhang Y**, Fujita N, Oh-hara T, Morinaga Y, Nakagawa T, Yamada M, Tsuruo T. Production of interleukin-11 in bone-derived endothelial cells and its role in the formation of osteolytic bone metastasis. *Oncogene* 1998; **16**: 693-703 [PMID: 9488033 DOI: 10.1038/sj.onc.1201581]
42 **Roodman GD**. Mechanisms of bone metastasis. *N Engl J Med* 2004; **350**: 1655-1664 [PMID: 15084698 DOI: 10.1056/NEJMra030831]
43 **Santini D**, Perrone G, Roato I, Godio L, Pantano F, Grasso D, Russo A, Vincenzi B, Fratto ME, Sabbatini R, Della Pepa C, Porta C, Del Conte A, Schiavon G, Berruti A, Tomasino RM, Papotti M, Papapietro N, Onetti Muda A, Denaro V, Tonini G. Expression pattern of receptor activator of NFκB (RANK) in a series of primary solid tumors and related bone metastases. *J Cell Physiol* 2011; **226**: 780-784 [PMID: 20857484 DOI: 10.1002/jcp.22402]
44 **Jones DH**, Nakashima T, Sanchez OH, Kozieradzki I, Komarova SV, Sarosi I, Morony S, Rubin E, Sarao R, Hojilla CV, Komnenovic V, Kong YY, Schreiber M, Dixon SJ, Sims SM, Khokha R, Wada T, Penninger JM. Regulation of cancer cell migration and bone metastasis by RANKL. *Nature* 2006; **440**: 692-696 [PMID: 16572175 DOI: 10.1038/nature04524]
45 **Blair JM**, Zhou H, Seibel MJ, Dunstan CR. Mechanisms of disease: roles of OPG, RANKL and RANK in the pathophysiology of skeletal metastasis. *Nat Clin Pract Oncol* 2006; **3**: 41-49 [PMID: 16407878 DOI: 10.1038/ncponc0381]
46 **Peters S**, Meylan E. Targeting receptor activator of nuclear factor-kappa B as a new therapy for bone metastasis in non-small cell lung cancer. *Curr Opin Oncol* 2013; **25**: 137-144 [PMID: 23283210 DOI: 10.1097/CCO.0b013e32835d720b]
47 **Scagliotti GV**, Hirsh V, Siena S, Henry DH, Woll PJ, Manegold C, Solal-Celigny P, Rodriguez G, Krzakowski M, Mehta ND, Lipton L, García-Sáenz JA, Pereira JR, Prabhash K, Ciuleanu TE, Kanarev V, Wang H, Balakumaran A, Jacobs I.

Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. *J Thorac Oncol* 2012; **7**: 1823-1829 [PMID: 23154554 DOI: 10.1097/JTO.0b013e31826aec2b]

48 **Gabr AG**, Goto H, Hanibuchi M, Ogawa H, Kuramoto T, Suzuki M, Saijo A, Kakiuchi S, Trung VT, Sakaguchi S, Moriya Y, Sone S, Nishioka Y. Erlotinib prevents experimental metastases of human small cell lung cancer cells with no epidermal growth factor receptor expression. *Clin Exp Metastasis* 2012; **29**: 207-216 [PMID: 22170031 DOI: 10.1007/s10585-011-9443-3]

49 **Guise TA**, Yin JJ, Taylor SD, Kumagai Y, Dallas M, Boyce BF, Yoneda T, Mundy GR. Evidence for a causal role of parathyroid hormone-related protein in the pathogenesis of human breast cancer-mediated osteolysis. *J Clin Invest* 1996; **98**: 1544-1549 [PMID: 8833902 DOI: 10.1172/JCI118947]

50 **Shen X**, Falzon M. PTH-related protein modulates PC-3 prostate cancer cell adhesion and integrin subunit profile. *Mol Cell Endocrinol* 2003; **199**: 165-177 [PMID: 12581888 DOI: 10.1016/S0303-7207(02)00287-3]

51 **Karaplis AC**, Goltzman D. PTH and PTHrP effects on the skeleton. *Rev Endocr Metab Disord* 2000; **1**: 331-341 [PMID: 11706747 DOI: 10.1023/A: 1026526703898]

52 **Yasuda H**, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki S, Tomoyasu A, Yano K, Goto M, Murakami A, Tsuda E, Morinaga T, Higashio K, Udagawa N, Takahashi N, Suda T. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. *Proc Natl Acad Sci USA* 1998; **95**: 3597-3602 [PMID: 9520411 DOI: 10.1073/pnas.95.7.3597]

53 **Lacey DL**, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, Elliott R, Colombero A, Elliott G, Scully S, Hsu H, Sullivan J, Hawkins N, Davy E, Capparelli C, Eli A, Qian YX, Kaufman S, Sarosi I, Shalhoub V, Senaldi G, Guo J, Delaney J, Boyle WJ. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 1998; **93**: 165-176 [PMID: 9568710 DOI: 10.1016/S0092-8674(00)81569-X]

54 **Kuo PL**, Liao SH, Hung JY, Huang MS, Hsu YL. MicroRNA-33a functions as a bone metastasis suppressor in lung cancer by targeting parathyroid hormone related protein. *Biochim Biophys Acta* 2013; **1830**: 3756-3766 [PMID: 23458685 DOI: 10.1016/j.bbagen.2013.02.022]

55 **Gong M**, Ma J, Guillemette R, Zhou M, Yang Y, Yang Y, Hock JM, Yu X. miR-335 inhibits small cell lung cancer bone metastases via IGF-IR and RANKL pathways. *Mol Cancer Res* 2014; **12**: 101-110 [PMID: 23966614]

56 **Sethi N**, Dai X, Winter CG, Kang Y. Tumor-derived JAGGED1 promotes osteolytic bone metastasis of breast cancer by engaging notch signaling in bone cells. *Cancer Cell* 2011; **19**: 192-205 [PMID: 21295524 DOI: 10.1016/j.ccr.2010.12.022]

57 **Santagata S**, Demichelis F, Riva A, Varambally S, Hofer MD, Kutok JL, Kim R, Tang J, Montie JE, Chinnaiyan AM, Rubin MA, Aster JC. JAGGED1 expression is associated with prostate cancer metastasis and recurrence. *Cancer Res* 2004; **64**: 6854-6857 [PMID: 15466172 DOI: 10.1158/0008-5472.CAN-04-2500]

58 **Chiba S**. Notch signaling in stem cell systems. *Stem Cells* 2006; **24**: 2437-2447 [PMID: 16888285 DOI: 10.1634/stemcells.2005-0661]

59 **Ye YZ**, Zhang ZH, Fan XY, Xu XL, Chen ML, Chang BW, Zhang YB. Notch3 overexpression associates with poor prognosis in human non-small-cell lung cancer. *Med Oncol* 2013; **30**: 595 [PMID: 23645556]

60 **Lawless MW**, O'Byrne KJ, Gray SG. Targeting oxidative stress in cancer. *Expert Opin Ther Targets* 2010; **14**: 1225-1245 [PMID: 20942747 DOI: 10.1517/14728222.2010.526933]

61 **Gabrilovich DI**, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. *Nat Rev Immunol* 2012; **12**: 253-268 [PMID: 22437938 DOI: 10.1038/nri3175]

62 **Nakashima T**, Takayanagi H. Osteoclasts and the immune system. *J Bone Miner Metab* 2009; **27**: 519-529 [PMID: 19455385 DOI: 10.1007/s00774-009-0089-z]

63 **Sawant A**, Deshane J, Jules J, Lee CM, Harris BA, Feng X, Ponnazhagan S. Myeloid-derived suppressor cells function as novel osteoclast progenitors enhancing bone loss in breast cancer. *Cancer Res* 2013; **73**: 672-682 [PMID: 23243021 DOI: 10.1158/0008-5472.CAN-12-2202]

64 **Roato I**, Gorassini E, Buffoni L, Lyberis P, Ruffini E, Bonello L, Baldi I, Ciuffreda L, Mussa A, Ferracini R. Spontaneous osteoclastogenesis is a predictive factor for bone metastases from non-small cell lung cancer. *Lung Cancer* 2008; **61**: 109-116 [PMID: 18061306]

65 **Colucci S**, Brunetti G, Rizzi R, Zonno A, Mori G, Colaianni G, Del Prete D, Faccio R, Liso A, Capalbo S, Liso V, Zallone A, Grano M. T cells support osteoclastogenesis in an in vitro model derived from human multiple myeloma bone disease: the role of the OPG/TRAIL interaction. *Blood* 2004; **104**: 3722-3730 [PMID: 15308561 DOI: 10.1182/blood-2004-02-0474]

66 **Roato I**, Grano M, Brunetti G, Colucci S, Mussa A, Bertetto O, Ferracini R. Mechanisms of spontaneous osteoclastogenesis in cancer with bone involvement. *FASEB J* 2005; **19**: 228-230 [PMID: 15550550]

67 **D'Amelio P**, Grimaldi A, Pescarmona GP, Tamone C, Roato I, Isaia G. Spontaneous osteoclast formation from peripheral blood mononuclear cells in postmenopausal osteoporosis. *FASEB J* 2005; **19**: 410-412 [PMID: 15611151]

68 **Zhang K**, Kim S, Cremasco V, Hirbe AC, Collins L, Piwnica-Worms D, Novack DV, Weilbaecher K, Faccio R. CD8+ T cells regulate bone tumor burden independent of osteoclast resorption. *Cancer Res* 2011; **71**: 4799-4808 [PMID: 21602433 DOI: 10.1158/0008-5472.CAN-10-3922]

69 **Schilbach K**, Geiselhart A, Handgretinger R. Induction of proliferation and augmented cytotoxicity of gammadelta T lymphocytes by bisphosphonate clodronate. *Blood* 2001; **97**: 2917-2918 [PMID: 11345090 DOI: 10.1182/blood.V97.9.2917]

70 **Wrzesinski SH**, Wan YY, Flavell RA. Transforming growth factor-beta and the immune response: implications for anticancer therapy. *Clin Cancer Res* 2007; **13**: 5262-5270 [PMID: 17875754 DOI: 10.1158/1078-0432.CCR-07-1157]

71 **Miossec P**, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *N Engl J Med* 2009; **361**: 888-898 [PMID: 19710487 DOI: 10.1056/NEJMra0707449]

72 **Cheran SK**, Herndon JE, Patz EF. Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. *Lung Cancer* 2004; **44**: 317-325 [PMID: 15140545 DOI: 10.1016/j.lungcan.2003.11.008]

73 **Terpos E**, Kiagia M, Karapanagiotou EM, Charpidou A, Dilana KD, Nasothimiou E, Harrington KJ, Polyzos A, Syrigos KN. The clinical significance of serum markers of bone turnover in NSCLC patients: surveillance, management and prognostic implications. *Anticancer Res* 2009; **29**: 1651-1657 [PMID: 19443381]

74 **Karapanagiotou EM**, Terpos E, Dilana KD, Alamara C, Gkiozos I, Polyzos A, Syrigos KN. Serum bone turnover markers may be involved in the metastatic potential of lung cancer patients. *Med Oncol* 2010; **27**: 332-338 [PMID: 19373566 DOI: 10.1007/s12032-009-9214-z]

75 **Brown JE**, Cook RJ, Major P, Lipton A, Saad F, Smith M, Lee KA, Zheng M, Hei YJ, Coleman RE. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J Natl Cancer Inst* 2005; **97**: 59-69 [PMID: 15632381 DOI: 10.1093/jnci/dji002]

76 **Lumachi F**, Santeufemia DA, Del Conte A, Mazza F, Tozzoli R, Chiara GB, Basso SM. Carboxy-terminal telopeptide (CTX) and amino-terminal propeptide (PINP) of type I collagen as markers of bone metastases in patients with non-small cell lung cancer. *Anticancer Res* 2013; **33**: 2593-2596 [PMID:

23749913]
77 **Weitzmann MN**, Roggia C, Toraldo G, Weitzmann L, Pacifici R. Increased production of IL-7 uncouples bone formation from bone resorption during estrogen deficiency. *J Clin Invest* 2002; **110**: 1643-1650 [PMID: 12464669 DOI: 10.1172/JCI0215687]
78 **Cenci S**, Weitzmann MN, Roggia C, Namba N, Novack D, Woodring J, Pacifici R. Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-alpha. *J Clin Invest* 2000; **106**: 1229-1237 [PMID: 11086024 DOI: 10.1172/JCI11066]
79 **Ryan MR**, Shepherd R, Leavey JK, Gao Y, Grassi F, Schnell FJ, Qian WP, Kersh GJ, Weitzmann MN, Pacifici R. An IL-7-dependent rebound in thymic T cell output contributes to the bone loss induced by estrogen deficiency. *Proc Natl Acad Sci USA* 2005; **102**: 16735-16740 [PMID: 16267136 DOI: 10.1073/pnas.0505168102]
80 **Colucci S**, Brunetti G, Cantatore FP, Oranger A, Mori G, Quarta L, Cirulli N, Mancini L, Corrado A, Grassi FR, Grano M. Lymphocytes and synovial fluid fibroblasts support osteoclastogenesis through RANKL, TNFalpha, and IL-7 in an in vitro model derived from human psoriatic arthritis. *J Pathol* 2007; **212**: 47-55 [PMID: 17370327 DOI: 10.1002/path.2153]
81 **Colucci S**, Mori G, Brunetti G, Coricciati M, Pignataro P, Oranger A, Cirulli N, Mastrangelo F, Grassi FR, Grano M. Interleukin-7 production by B lymphocytes affects the T cell-dependent osteoclast formation in an in vitro model derived from human periodontitis patients. *Int J Immunopathol Pharmacol* 2005; **18**: 13-19 [PMID: 16848983]
82 **Roato I**, Brunetti G, Gorassini E, Grano M, Colucci S, Bonello L, Buffoni L, Manfredi R, Ruffini E, Ottaviani D, Ciuffreda L, Mussa A, Ferracini R. IL-7 up-regulates TNF-alpha-dependent osteoclastogenesis in patients affected by solid tumor. *PLoS One* 2006; **1**: e124 [PMID: 17205128 DOI: 10.1371/journal.pone.0000124]
83 **Roato I**, Gorassini E, Brunetti G, Grano M, Ciuffreda L, Mussa A, Ferracini R. IL-7 modulates osteoclastogenesis in patients affected by solid tumors. *Ann N Y Acad Sci* 2007; **1117**: 377-384 [PMID: 17584976 DOI: 10.1196/annals.1402.002]
84 **Giuliani N**, Colla S, Sala R, Moroni M, Lazzaretti M, La Monica S, Bonomini S, Hojden M, Sammarelli G, Barillè S, Bataille R, Rizzoli V. Human myeloma cells stimulate the receptor activator of nuclear factor-kappa B ligand (RANKL) in T lymphocytes: a potential role in multiple myeloma bone disease. *Blood* 2002; **100**: 4615-4621 [PMID: 12393684 DOI: 10.1182/blood-2002-04-1121]
85 **Roato I**, Caldo D, Godio L, D'Amico L, Giannoni P, Morello E, Quarto R, Molfetta L, Buracco P, Mussa A, Ferracini R. Bone invading NSCLC cells produce IL-7: mice model and human histologic data. *BMC Cancer* 2010; **10**: 12 [PMID: 20067635 DOI: 10.1186/1471-2407-10-12]

P- Reviewers: Hida T, Watanabe A **S- Editor**: Zhai HH
L- Editor: Cant MR **E- Editor**: Liu SQ

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza, 315-321 Lockhart Road,
Wan Chai, Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com